III. REMARKS

A. Status of the Claim

Claims 1-13, 18-19, 21-23, 31-32, and 37-40 are currently pending and encompass the elected species.

B. Information Disclosure Statement

The Office Action mailed on October 26, 2010 recited on page 2 that "[r]eferences lined-through on the information disclosure statement(s) were not considered because they were not provided, were not provided in English, or did not have a proper publication date."

In the response filed on November 24, 2010, Applicants respectfully noted that Form PTO-1449s returned with the Office Action mailed on October 26, 2010 did not contained any references which were lined-through, and requested that the Examiner confirms that all of the references listed on the returned Form PTO-1449s were considered.

The present Office Action did not contain such a confirmation.

Applicants respectfully request that the Examiner confirms in the next Office Communication that all of the references listed on the Form PTO-1449s returned with the Office Action of October 26, 2010 were considered.

C. Abstract

The Abstract of the disclosure is objected to. The Examiner states on page 3 of the Office Action that "[a] new abstract should be provided that includes more detail than

is currently present." The Examiner further states that "[e]xpanding the abstract past its current one-sentence format would be helpful."

In response, Applicants submit herewith a Replacement Abstract. The Replacement Abstract recites:

> *Abuse resistant opioid transdermal delivery device containing opioid antagonist microspheres dispersed in an opioid agonist containing layer. The opioid antagonist is not releasable from the transdermal delivery device applied topically intact to a skin of a human patient, and is releasable from the transdermal delivery device which is administered intraoraly, chewed, soaked, punctured, or torn.*

Support for the replacement abstract can be found, e.g., in paragraphs [0012], [0020] and [0024] of the specification.

It is respectfully submitted that no new matter is being added by the replacement abstract.

Withdrawal of the objection is respectfully requested.

D. Claim Rejections- 35 U.S.C. § 103

1. The combination of the Granger patent, the Sackler publication and the McGinity patent

Claims 1, 2, 5-13, 18, 19, 21-23, 31, 32, 39, and 40 have been rejected under 35 U.S.C. § 103(a) over the combination of U.S. Patent No. 5,149,538 to Granger et al. ("the Granger patent"), U.S. 2003/0068392 to Sackler ("the Sackler publication") and U.S. Patent No. 5,288,505 to McGinity et al. ("the McGinity patent"). The Examiner states on page 5 of the Office Action that "Granger does not elaborate on the internal structure of the antagonist particles" and that "the ordinary artisan would have reason to look to the literature for the guidance as to the composition of the antagonist particles." The

Examiner relies on the McGinity patent for the teaching of multi-phase microspheres containing a microemulsion. See Office Action, page 6.

The rejection is respectfully traversed.

Applicants respectfully submit that the skilled person looking to solve the problem addressed in the present application (i.e., abuse of transdermal delivery devices comprising opioid agonists) would not have a reason to look to the McGinity patent because the McGinity patent is neither directed to transdermal delivery of active agents nor is concerned with a reduction of an abuse potential of a transdermal delivery device comprising an opioid agonist. In fact, there is no mention of transdermal delivery, no mention of opioid agonists, and no mention of opioid antagonists in the McGinity patent.

Even if the skilled person were to look at the McGinity patent, the skilled person would have realized, based on the disclosure of the McGinity patent, that the microspheres described therein would not be suitable for rendering transdermal delivery devices misuse resistant as described in the Granger patent.

The Granger patent states that the transdermal dosage form of Granger "provides the benefit of being resistive to misuse because the opioid antagonist is released from the dosage form upon being ingested or substantially immersed in water or other solvents." See col. 1, line 66, to col. 2, line 2. The Granger patent further states that its impermeable barrier "prevent[s] release of the antagonist unless the dosage form is ingested or immersed in water, alcohol or other solvent." See col. 2, ll. 24-60. Applicants respectfully submit that based on this disclosure the skilled person would have realized that to "substantially attenuate the euphorigenic effect of the opioid, thereby reducing the tendency for misuse and abuse of the dosage form" as described in the Granger patent, the opioid antagonist would have to be released from the dosage form quickly upon ingestion or immersion of the dosage form in water, alcohol or other solvent, before an abuser can extract the opioid agonist. See col. 2, ll. 61-64.

The McGinity patent describes "slow releasing multi-phase microspheres," rather than microspheres which release the active quickly. See col. 12, l. 57. The McGinity patent emphasizes that the multiple emulsion technique used in the preparation of its multi-phase microspheres "enhance[s] the slow release characteristic of the compound from the microsphere." See, e.g., col. 12, ll. 55-69. The McGinity patent further states that "delivery of the molecular compound may be achieved for an average of three months in vivo with the described multi-phase microspheres" and "that the multi-phase microspheres may be formulated to provide delivery in vivo of the agent for up to 1 year." See col. 8, ll. 56-62. Applicants submit that the skilled person would have realized that the slow release for a prolonged period of time for up to 1 year is not the much quicker release contemplated by the Granger patent.

The skilled person therefore would have realized that the microspheres described in the McGinity patent are not suitable for providing the contemplated release of the Granger patent, and would therefore not have used the microspheres described in the McGinity patent in formulating misuse-resistant transdermal delivery devices described in the Granger patent, especially because there is no mention of transdermal delivery, opioid agonist or opioid antagonist in the McGinity patent.

Because there is no mention of transdermal delivery, opioid agonist or opioid antagonist in the McGinity patent, the result of incorporating the microspheres of the McGinity patent into the transdermal delivery system of the Granger patent cannot provide an expectation that the combination would have worked for its intended purpose. According to the Examiners' Summary for Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex:

> *Predictability as discussed in KSR encompasses ... the expectation that the combination would have worked for its intended purpose ...*

See page 37.

In the present case, because the McGinity patent contemplates "slow release" of the active agent from its microspheres, the McGinity patent would not have provided an

expectation that the structure of its "slow releasing" microspheres was suitable for achieving the intended purpose of quick release of the opioid antagonist.

Applicants further submit that the rejection is improper because there is no connection between the microspheres described in the McGinity patent and the misuse-resistant transdermal delivery dosage forms comprising an opioid agonist and an opioid antagonist described in the Granger patent and the Sackler publication. The skilled person therefore would have had no reason to look to the McGinity patent and to formulate a transdermal delivery device based on a combination of the McGinity patent, the Granger patent and the Sackler publication.

For the foregoing reasons, Applicants submit that the combination of the cited references cannot render obvious claims 2, 5-13, 18, 19, 21-23, 31, 32, 39, and 40.

With further regard to claim 1, Applicants submit that the combination of cited references does not teach or suggestion a transdermal delivery system comprising a microsphere comprising a microemulsion of an opioid antagonist as recited in claim 1, as there is no mention of a microemulstion of an opioid antagonist anywhere in the cited references.

With further regard to claim 5, and in response to the Examiner's statement on page 7 of the Office Action that "Granger teaches that the opioid drug is dispersed in a polymeric matrix (delivery means) (col. 3, line 48[,] to col. 4, line 20)," Applicants respectfully point out that this description in the Granger patent is with regard to the opioid delivered through the skin (i.e., opioid agonist), rather than an opioid antagonist to be retained in the transdermal delivery device applied topically intact to a skin of a human patient. Accordingly, this disclosure cannot render obvious present claim 5.

With further regard to claims 9 and 10, and in response to the Examiner's statement that "the particular size ranges in any given claim do not appear to be critical to the essential function of the invention," Applicants respectfully point out that the

specification states in paragraph [0016] that, in an embodiment of microspheres in a mean size of from about 1 to about 500 μm, the opioid antagonist microspheres of this size "will not be easily separated from the opioid agonist by an abuser in an attempt to abuse the opioid agonist contained in the transdermal device." The size ranges in claims 9 and 10 are therefore important in the claimed invention. Because there is nothing in the cited references that suggests that microspheres in a mean size of from about 1 to about 500 μm "will not be easily separated from the opioid agonist by an abuser in an attempt to abuse the opioid agonist contained in the transdermal device," the cited references cannot render obvious the selection of this size range.

With further regard to claims 39 and 40, and in response to the Examiner's statement on page 9 of the Office Action that "Sackler establishes the functional equivalence of poly(lactic/glycolic acid) ("PLGA"), polylactides, polyglycolides, polyorhtoesters, polycaprolactones, and mixtures or blends of any of these (par. [0096])," Applicants respectfully point out that paragraph [0096] of the Sackler publication is directed to "[t]he pharmaceutically acceptable hydrophobic material useful for preparing an aversive agent ...," rather than an opioid antagonist. Applicants further note that, according to paragraph [0033] of the Sackler patent, "[t]he term 'aversive agent' is defined ... to mean a bittering agent, an irritant, or a gelling agent." Paragraph [0096] of the Sackler publication cannot therefore establish the purported functional equivalency of poly(e)caprolactone and the barrier means described in the Granger patent, as it does not mention opioid antagonists.

In response to the Examiner's statement on page 10 of the Office Action that "there is no structural difference that would prevent Granger's devices from releasing the antagonist intraorally (i.e., within the mouth)," Applicants respectfully submit that the Granger patent states that the barrier means "prevent[s] release of the antagonist unless the dosage form is ingested or immersed in water, alcohol or other solvent." See col. 2, ll. 54-64. The Granger patent therefore purports that the type and the amount of the barrier means is such that the antagonist is not released from its particles unless the dosage form is "ingested or immersed in water, alcohol or other solvent."

In response to the Examiner's rhetorical question page 10 of the Office Action (does the fact that the Granger patent does not explicitly use the word "intraoral" mean that Granger's devices are incapable of releasing the antagonist in the oral cavity such as when as when the transdermal patch is sucked by the abuser?") and the answer provided by the Examiner, Applicants respectfully submit that the test for obviousness is what the cited references would have suggested to the skilled person. Here, the Granger patent explicitly states in col. 2, ll. 54-64, that "the antagonist is not released unless the dosage form is "ingested or immersed in water, alcohol or other solvent." Because sucking a dosage form does not constitute ingestion or immersion in water, alcohol or other solvent, the Granger patent suggests that sucking the transdermal dosage form of Granger will not result in the release of the antagonist.

In response to the Examiner's statement on page 10 of the Office Action that "[i]ngestion reasonably reads on 'intraoral,'" Applicants respectfully disagree, noting that the term "intraoral" means "within the mouth," whereas "ingestion" implies swallowing of the dosage form. The term "ingestion" does not include intraoral administration.

In response to the Examiner's request on page 11 that Applicants explain "how intraoral administration does not constitute 'substantial immersion' in an aqueous liquid," Applicants respectfully note that the amount of saliva that the dosage form is exposed to in the oral cavity may be substantially less than the amount the dosage form is exposed to upon "substantial immersion." According to the Gale publication, which was cited in the previous Office Action (U.S. 2004/0013716), showering does not constitute "substantial immersion" in a solvent. See, e.g., par. [0072] ("... that antagonist reservoir 3 comprises an antagonist in a substantially non-releasable form when the transdermal delivery system is used as recommended and/or incidental exposure to water (e.g., sweat, showering, high humidity etc.), the antagonist being releasable from the analgesic system ... upon being ingested or substantially immersed in a solvent") (underlining added). Because showering does not constitute "substantial immersion" in water, it is reasonable

to conclude that exposure of a dosage form in an oral cavity also would not constitute "substantial immersion" in water.

In response to the Examiner's statement on page 11 of the Office Action that "*any* behavior or environment that results in aqueous fluids (or other solvents such as alcohol) penetrating into the substantially anhydrous matrix containing the antagonist particles with result in the release of the antagonist" from the Granger's device, Applicants respectfully note that the Granger patent states that the barrier means "prevent[s] release of the antagonist unless the dosage form is ingested or immersed in water, alcohol or other solvent" (underlining added). See col. 2, ll. 54-64. The Examiner's assertion contradicts the explicit teaching of the Granger patent.

The Examiner has stated (page 11 of the Office Action) that "Granger's failure to describe the antagonist release scenarios in more detail can be attributed to the fact that there are myriad ways in which drug abusers can attempt to remove an opioid drug from a transdermal patch, and an inventor cannot possibly be expected to list all (or even most) of them." In response, Applicants respectfully note that the Granger patent is very specific in describing the problem it is addressing. The Granger patent states:

> *The dosage forms of the prior art have deficiencies in that an addict can extract the narcotic from the dosage form for injection or ingestion, or that the narcotic and antagonist are physically combined such that adverse physical and chemical interaction may occur. The present invention overcomes the deficiencies of the prior art dosage forms by providing a transdermal dosage form containing an opioid and an opioid antagonist, wherein the opioid and the antagonist are physically separated by an impermeable barrier ... The dosage form of this invention further provides the benefit of being resistive to misuse because the opioid antagonist is released from the dosage form upon being ingested or substantially immersed in water or other solvents. When applied to the skin, the dosage form of this invention delivers only the opioid through the skin and into the systemic circulatory system.*

Col. 1, l. 55, to col. 2, l.5.

Applicants submit that had Granger et al. contemplated any form of abuse other than the extraction described in the Granger patent, then they would have clearly included a general statement about abuse of transdermal devices containing opioid agonists, which they did not do.

In response to the Examiner's reference to Van Duren (U.S. 2004/0191301), which states that "[o]ne disadvantage of this design [the design of the Granger patent] is the soluble barrier, which may release the antagonist prematurely if the patch gets wetted accidentally, or is disposed in a humid environment, such as when a user showers or bathes," Applicants submit that this statement does not establish or suggest that the antagonist of Granger will be released if placed in an oral cavity of a human patient.

In any event, Applicants respectfully submit that instant claim 1, which recites in part that the opioid antagonist "is releasable from the transdermal delivery device administered intraorally," specifies that the antagonist microspheres comprise "a microemulsion of an opioid antagonist." The Examiner has acknowledged on page 12 of the Office Action that the feature of the microemulsion of an opioid antagonist is not disclosed in the Granger patent. As stated above, this feature is missing from the disclosure of the Sackler publication and the McGinity patent. The combination of the cited references cannot render this feature obvious.

Reconsideration and withdrawal of the rejection is respectfully requested.

2. The combination of the Granger patent, the Sackler publication, the McGinity patent and the Ravivarapu article

Claims 3, 4, 37, and 38 have been rejected over the combination of the Granger patent, the Sackler publication, the McGinity patent, and Ravivarapu et al. Pharm. Dev. Tech. (2000), 5(2); 287-296 ("the Ravivarapu article"). The Ravivarapu article has been relied on by the Examiner for the teaching of calcium chloride in the microsphere.

The rejection is respectfully traversed for the reasons given above with respect to the obviousness rejection over the combination of the Granger patent, the Sackler publication, the McGinity patent.

Applicants further submit that there is no mention of opioid antagonist or transdermal delivery devices in the Ravivarapu article. The Ravivarapu article cannot therefore teach or suggest that calcium chloride is suitable for incorporation into an opioid-containing microsphere or a transdermal delivery device; and therefore does not provide any reason for the skilled person to formulate a transdermal delivery device comprising a microsphere comprising an opioid antagonist and calcium chloride as recited in claim 3.

Reconsideration and withdrawal of the rejection is respectfully requested.

E. Double Patenting

Claims 1-13, 18, 19, 21-23, 31, and 32 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-33 of copending application No. 11/865,387, in view of the Granger patent, the Sackler publication, the McGinity patent, and the Ravivarapu article.

Applicants respectfully submit that the rejection is improper for the reasons given above in response to the obviousness rejection.

Applicants further submit that the Manual of Patent Examining Procedure states:

> *If a 'provisional' nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that application to issue as a patent without a terminal disclaimer.*

MPEP, section 804.

The present application was filed on February 15, 2005, as International Application No. PCT/US2008/0233178, before the filing date of copending application No. 11/865,387, which was filed on October 1, 2007. As of August 24, 2011, the claims of the '387 application were subject to an obviousness rejection.

Withdrawal of the provisional double patenting rejection in the present application is therefore warranted if the obviousness rejections discussed above are withdrawn.

Withdrawal of the provisional rejection is respectfully requested.

IV. Conclusion

An allowance of the present application is earnestly solicited. The Examiner is respectfully invited to contact the undersigned at the telephone number provided below if he believes that a telephonic interview will advance the prosecution of the present application.

Respectfully submitted,
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